THYROID DYSFUNCTION AND INFERTILITY OF WOMEN OF REPRODUCTIVE AGE

Abstract

Autoimmunity of the thyroid gland (TAI) or its dysfunction is quite common among women of reproductive age, and there are suggestions in the literature that they are associated with an unfavorable level of fertility and a negative outcome of pregnancy, as in the case of spontaneous conception or after **assisted reproductive technologies** (ART).

This assumption makes it necessary to screen autoantibodies to thyrotropin (TSH) and thyroid peroxidase among infertile women who have made a number of attempts to become pregnant.

Some authors have conducted a number of studies where they have examined the relationship between autoimmunity of the thyroid gland, thyroid function, and fertility. However, there is currently no consensus on the upper limit of the norm for TSH to determine thyroid dysfunction and the limits for intervention. Despite the recent update of the American thyroid Association (ATA) on guidelines for the diagnosis and treatment of thyroid diseases during pregnancy and the postpartum period, many issues remain unresolved in ART.

Keywords: thyroid, autoimmunity, infertility, assisted reproductive technologies

Introduction

Birth is a fundamental evolutionary process for sustaining life. In this regard, it is very important to take into account the complex regulatory endocrine and immune factors that determine fertility and implantation.

The international committee for monitoring assisted reproductive technologies (ICMART) and the world health organization (WHO) define infertility (clinical definition) in the revised Glossary of ART terminology "as a disease of the reproductive system defined by the inability to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [3]."

It has been determined that approximately one in six of all couples will have difficulty conceiving (primary infertility) or conceiving the desired number of children (secondary infertility) [8]. The world health organization (WHO) task force on infertility diagnosis and treatment conducted a study of 8,500 infertile couples in developed countries [9]. Female-related infertility accounted for 37%, and combined male and female factors accounted for 35% of the causes of infertility. The most common causes of female infertility were: ovulation disorders (25%), endometriosis (15%), pelvic adhesions (12%), blocked fallopian tubes (11%), other tube abnormalities (11%), and hyperprolactinemia (7%).

When faced with fertility problems, couples often seek help from fertility specialists. Over the past two decades, the field of fertility has been studied quite intensively, and researchers have tried to identify curable risk factors that contribute to infertility. These risk factors include the presence of thyroid autoimmunity and thyroid dysfunction. Consequently, screening for TSH and anti-thyroperoxidase antibodies is usually a part of the initial study [5].

Methods of research

In this work, we have studied the literature related to the problem of the effect of thyroid dysfunction on female infertility. Comparative and analytical research methods were applied.

Results and discussion

Literature analysis showed a high prevalence of thyroid disorders (dysfunction and autoimmunity) among women of reproductive age [11]. The incidence of hypothyroidism ranges from 2% to 4% and is largely due to autoimmune thyroid disease (TAI) [12].

Subclinical thyroid abnormalities, including subclinical hypothyroidism, hypothyroxinemia, and / or isolated TAI, are much more common than clinical thyroid dysfunction.

The importance of thyroid hormones has been emphasized since the discovery of TSH, its receptors, and thyroid hormone receptors (TR-α1 and TR-β1) on the epithelium of the ovarian surface and in the oocytes of the primary, and secondary follicles [12]. Thyroid hormones appear to be involved in the complex regulation of ovarian function. Thyroid hormones can also indirectly affect aspects of fertility by altering gonadotropin-releasing hormone (GnRH) and prolactin secretion, levels of sex hormone-binding globulin (SHBG), and coagulation factors.

Taking into account the importance of thyroid hormones, even mild thyroid insufficiency has been identified as one of the possible causes of adverse fertility and pregnancy outcomes.

The extent to which hyperthyroidism is associated with fertility problems is not clearly established due to limited data in the literature. However, in general, in the absence of adequate treatment, hyperthyroidism is associated with early pregnancy loss [11].

Thyrotoxicosis increases serum levels of sex hormone-binding globulin (SHBG) and estradiol (E2) compared to euthyroid women. The latter may be the result of an increase in SHBG or an increase in the production of E2 and

androgen in combination with an increase in the degree of conversion to estrone and E2. In addition, LH secretion is increased among patients with Graves ' disease compared to patients with euthyroidism [12].

Some authors have noted that primary or secondary infertility occurs among 5.8% of patients with hyperthyroidism [14]. Menstrual disorders are common among women with hyperthyroidism. Early data indicate menstrual irregularities of up to 65%, compared with 17% of healthy people in the control group [11]. More recent data showed a significantly lower prevalence of menstrual disorders - about 22% compared to 8% of healthy people in the control group [5]. This contradiction is related to different approaches to the diagnosis and treatment of clinical hyperthyroidism. Hypomenorrhea, polymenorrhea, oligomenorrhea, and hypermenorrhea are the most common disorders of the menstrual cycle.

Open hypothyroidism is associated with an increased risk of fertility problems and adverse complications of early and late pregnancy [13]. Hypothyroidism leads to a number of hormonal changes. The rate of metabolic clearance of both Androstenedione and estrone decreases, and peripheral aromatization increases. In addition, SHBG plasma binding activity is reduced. Consequently, plasma concentrations of both total testosterone and E2 decrease, and their unbound fraction increases.

Hypothyroidism can also lead to a blunted LH response, which stimulates TRH secretion and increases serum prolactin levels. Since prolactin impairs the pulsating secretion of gonadotropin-releasing hormone (GnRH), this can lead to ovulation dysfunction, including yellow body insufficiency with low levels of progesterone secretion in the luteal phase of the cycle [10]. Therefore, clinical hypothyroidism leads to a number of ovulation disorders among women of fertile age. There may be changes in the length of the cycle, as well as in the volume of menstrual bleeding secondary to breakthrough bleeding after anovulation and / or violation of hemostatic factors associated with hypothyroidism.

Most authors do not always link subclinical hypothyroidism (SCH) and infertility. This may be partly due to different thresholds used to determine the upper limit of normal TSH concentration, as well as the lack of well-planned prospective studies.

In a large retrospective cross-sectional study of 11,254 women in Denmark, impaired fertility was associated with subclinical hypothyroidism, defined as TSH> 3.7 Mme / l [26]. A recent cross-sectional study also showed higher normal TSH levels in women with unexplained infertility compared to the fertility control [17].

Based on these data, it can be said that the levels of TSH used in various studies to determine the relationship of thyroid function with fertility problems varied significantly. In general, the Association with adverse fertility outcomes appears to occur at TSH levels above 4.0 Mme / l.

TAI is the most common autoimmune disease of women of childbearing age and increases the risk of thyroid dysfunction. The prevalence of TAI is usually estimated at about 10% and is more common in women seeking infertility consultation [14].

Other causes of infertility have also been linked to TAI. Women with polycystic ovary syndrome (PCOS) were found to have an increased prevalence of TAI. A possible explanation may be polymorphisms of the PCOS-related fibrillin 3 gene, which affects the activity of TGF-β, a key regulator of immune tolerance.

Together with lower TGF-β, low vitamin D levels, and a high estrogen-to-progesterone ratio, these factors may contribute to autoimmunity [19].

As for endometriosis, the data are more contradictory, with conflicting results of increased prevalence of TAI [17]. There is evidence that endometriosis is associated with various immunological changes, including antibodies to endometrial antigens.

In general, high levels of TPO-abs have been identified as the most sensitive marker of TAI and are associated with the risk of subclinical hypothyroidism [5]. Therefore, most studies examining the prevalence of TAI among fertile women or any association between TAI and pregnancy outcomes are based on the presence of only TPO-abs and do not take into account autoantibodies to thyroglobulin (Tg-abs).

Also in the literature, the Association of TAI with adverse pregnancy outcomes, with an increased risk of miscarriage and premature birth in spontaneous pregnancy, as well as in pregnancy after ART. Since the late 1990s, several studies have been published on the effects of TAI on post-ART outcomes. The results of these studies, however, are contradictory, probably due to different study plans, a small number of registered patients with a low absolute number of analyzed events, and the use of surrogate endpoints for the fertility result (table 1).

Research by Zhong et al. comparison of IVF results in TAI-positive and TAI-negative women showed that TAI-positive women had significantly lower fertilization (64.3% vs. 74.6%), implantation (17.8% vs. 27.1%), and pregnancy rate (33.3% vs. 46.7). %) and a higher risk of pregnancy termination (26.9 vs. 11.8%) after IVF compared to their negative TAI counterparts. Two meta-analyses showed an increase in the frequency of miscarriages of TAI-positive women with subfertility. In the first meta-analysis of four prospective studies conducted by Toulis, women with TAI were twice as likely to experience a miscarriage after IVF pregnancy.

Table 1

Main characteristics of research on the relations between TAI and IVF / ICSI results.

Author	Year	Design of the study	Purpose of the study	Tests of the thyroid gland	TAI Number +	TAI Number -	State of the thyroid function	Main conclusion
Muller et al.	1999	Retrospective cohort study	LBR; CPR; Г-Н	TPOAbs; Tg Abs	143	730	euthyroid	Does not affect the outcome of pregnancy
Poppe et al.	1999	Prospective cohort study	CPR; Г-Н; OPR	TPOAbs	25	148	euthyroid	Does not affect the outcome of pregnancy
Negro et al.	2003	Prospective cohort study	LBR; CPR; Г-Н	TPOAbs	32	202	euthyroid	Lower LBR; increased MR
Negro et al.	2005	Prospective cohort study	LBR; CPR; Г-Н; NOR	TPOAbs	43	576	euthyroid	Lower LBR; does not affect CPR
Kilic et al.	2007	Retrospective cohort study	LBR; CPR; Г-H; NOR	TPOAbs	42	374	euthyroid	Does not affect the outcome of pregnancy
Zhong et al.	2008	Prospective cohort study	CPR; Г-H; NOR	TPOAbs; Tg Abs	23	31	euthyroid	below CPR
Karacan et al.	2012	Retrospective cohort study	CPR; Г-H; ИК; NOR; FR	TPOAbs; Tg Abs	90	676	Не указано	below CPR, FR, IR and above MR
Mintziori et al.	2013	Prospective cohort study	NOR; FR; ИК; CPR; Г-H; OPR	TPOAbs; Tg Abs	34	219	euthyroid	Does not affect the outcome of pregnancy
Tan et al.	2014	Retrospective cohort study	LBR; NOR; CPR; Г-H	TPOAbs; Tg Abs	15	67	euthyroid	Does not affect the outcome of pregnancy
Chai et al.	2014	Retrospective cohort study	LBR; CPR; Г-H	TPOAbs; Tg Abs	110	725	euthyroid	Does not affect the outcome of pregnancy
Lukasuk et al.	2014	Retrospective cohort study	LBR; CPR; Г-H	TPOAbs; Tg Abs	89	419	euthyroid	Does not affect the outcome of pregnancy
Litwicka et al.	2015	Retrospective cohort study	LBR; CPR; Г-H; NOR; infrared	TPOAbs	114	551	euthyroid	Does not affect the outcome of pregnancy
Sakar et al.	2015	Prospective cohort study	LBR; CPR; MR, NOR	TPOAbs; Tg Abs	60	134	euthyroid	Lower LBR; increased MR
Unuane et al.	2016	Prospective cohort study	CPR; OPR; Г-H; NOR	Не указано	49	202	unspecified	Does not affect the outcome of pregnancy
Muller et al.	2016	Retrospective cohort study	LBR; CPR; Г-H	TPOAbs	333	2019	euthyroid	Does not affect the outcome of pregnancy

*LBR = lifetime fertility rate; CPR = clinical pregnancy rate; OPR = current pregnancy; MR = miscarriage rate; IR = implantation rate; NOR = number of oocytes extracted; FR = fertilization rate

The actual difference in the number of miscarriages between euthyroid women with TAI who underwent IVF and the control group (absolute risk) remained small, which led to a negligible impact on the frequency of clinical pregnancies and deliveries.

In the second meta-analysis of 12 studies, the risk of miscarriage was significantly higher among women with TAI, resulting in a lower birth rate [5]. However, the amount of TAI did not affect the number of eggs extracted and the frequency of fertilization.

More recent studies on this topic have not been able to confirm the link between TAI and their negative impact on fertility. In a retrospective study, Lukaszuk et al. compared pregnancy outcome between 114 TAI-positive and 495 TAI-negative infertile women. No significant differences were found in fertilization, implantation, pregnancy rates, live birth, or higher risk of miscarriage [13]. A prospective study by Sakar et al. showed comparable rates of pregnancy and miscarriage between 49 positive and 202 negative women after IVF [14].

According to Tan et al. any previous association between TAI-positive women and a negative pregnancy outcome may be confused due to selection bias, particularly the choice of female patients who seek treatment for fertility problems. To avoid this bias, the author selected couples with male infertility and studied female partners with TAI, but without known female infertility. They found that the pregnancy outcome was comparable among women with and without thyroid autoimmunity after intracytoplasmic sperm injection [15].

The main pathophysiological mechanisms that link the possible negative impact of TAI on the outcome of pregnancy after ART remain unknown. The presence of TAI may represent a peripheral marker of a general immune imbalance, which can lead to insufficient fertilization, insufficient implantation, and prolonged pregnancy. The mechanism by which TAI can act is a change in endometrial susceptibility that affects the fetal allograft. Quantitative and qualitative changes in the profile of endometrial T cells with reduced IL-4 and IL-10 secretion along with increased interferon-γ secretion have been reported [11].

Hyperactivity and increased migration of cytotoxic natural killer cells can also alter the immune and hormonal response of the uterus in women with TAI. Compared to women who have had one or no miscarriages, women with multiple miscarriages appear to have an increased number of CD5 / 20 + B cells with a higher prevalence in women with thyroid antibodies [16]. Activation of polyclonal B cells is more often observed in TAI and is associated with an increase in the titers of inorganic specific autoantibodies. Limited data indicate the presence of antiphospholipid (APL) and / or anti-nuclear (ANA) antibodies in the population of infertile women with TAI [14]. Anti-lupus antibodies and anti-cardiolipin antibodies are significantly more common in women with infertility. In general, the influence of various associated autoimmune diseases on reproductive health indicators is largely ignored, and it requires further study [14].

Alternatively, anti-thyroid antibodies may be the direct cause, since the presence of anti-thyroid antibodies can have an adverse effect on the quality of oocytes and embryos. Indeed, the authors also found significantly lower oocyte fertilization and the percentage of class A embryos when comparing infertile women who underwent IVF with thyroid autoimmunity with negative controls [17]. For the first time, this study documented the presence of thyroid antibodies in ovarian follicular fluid. The authors suggested that thyroid antibodies may pass the "follicle-blood" barrier during secondary follicle maturation. The cytotoxicity of these antibodies can then damage the maturing oocyte and ultimately reduce oocyte quality and fertilization potential.

On the other hand, a positive TAI status increases the risk of developing (sub) clinical hypothyroidism. Women with TAI have an increased risk of developing (sub) clinical hypothyroidism during spontaneous pregnancy [18]. In the case of assisted reproductive technology (ART) and ovarian hyperstimulation, it has been reported that TSH levels rise significantly to levels above 2.5 Mme / l before pregnancy, and even more so in the presence of TAI [6]. Since thyroid hormones play an important role in oocyte maturation and implantation, it has been suggested that a decrease in thyroid function caused by the stimulation Protocol in women with TAI may negatively affect the pregnancy rate during ART.

In the literature there are also studies on approaches to treating hypothyroidism in order to increase fertility in women. Detailed information about the effect of hypothyroidism on the results of controlled ovarian hyperstimulation (HOG) and IVF is limited, as there are no available randomized controlled trials. The reason lies in the unethical question of refusing treatment to patients with clinical obvious hypothyroidism. Numerous negative effects of maternal overt hypothyroidism on pregnancy outcomes and adverse neurocognitive effects of offspring have been documented in the literature [11]. Treatment of hypothyroidism with levothyroxine usually restores normal menstrual structure, eliminates hormonal changes, and improves fertility [10]. However, some women with treated hypothyroidism still cannot get pregnant and seek infertility treatment, including controlled ovarian hyperstimulation and / or IVF. Treatment of apparent hypothyroidism in pregnant women is mandatory and includes levothyroxine therapy adapted to achieve normal trimester serum levels that stimulate thyroid-stimulating hormone (TSH).

The latest ATA recommendations call for achieving TSH concentrations below 2.5 Mme / l in patients with clinical hypothyroidism. An absolute inability to produce thyroid hormones during COX can actually have a detrimental effect on the oocyte and / or endometrium. However, the level of TSH that should be reached before starting ART remains controversial.

A meta-analysis of 3 RCTS showed a positive effect of levothyroxine treatment on pregnancy after ART in women with subclinical hypothyroidism [13]. Although no benefit was shown for clinical pregnancy rates (combined relative risk 1.75, 95% CI 0.90–3.38), there was an increase in delivery rates (combined relative risk 2.76, 95% CI 1.20–6.44). However, the included studies differed with respect to the upper TSH limit for determining SCH. This limit often exceeded 4 Mme / l. In fact, most of the available data conclude that there is no difference in the outcome of ART in women with euthyroid disease with TSH levels <2.5 Mme / l and in women with a slight increase in TSH levels from 2.5 to 5.0 Mme / l [12].

The use of appropriate control ranges should be based on local control values for the population and laboratory. Moreover, in pregnancy, in accordance with the ATA recommendations, it is recommended to use TSH concentrations based on reference ranges typical for pregnancy [21]. If this is not possible, it is recommended to use a fixed upper limit of 4.0 MMU / l, which usually corresponds to a decrease of 0.5 MMU / l compared to the negligent TSH reference range. These recommendations for the diagnosis and treatment of SCH seem reasonable in the case of ART, since adverse events were mainly reported in patients with TSH values above 4.0 Mme / l.

We have studied four randomized controlled trials that evaluated the effect of levothyroxine treatment in STH on various aspects of spontaneous pregnancy outcomes. Thus, some authors have noted that treatment with levothyroxine improved adverse pregnancy outcomes in women with a positive response to TPO, the level of TSH exceeded 2.5 Mme / l [15].

In another study, there was also a decrease in preterm birth in women with a positive response to TPO when treated with levothyroxine, but only in patients with TSH levels exceeding 4.0 Mme / l [16]. The same authors also confirmed only the positive effect of LT4 therapy in reducing preterm birth in women with a negative reaction to TPO and TSH levels above 4 Mme / l.

In a meta-analysis presented in one of the studies, a subgroup analysis involving two studies the effect of non-intervention treatment for SCH on the risk of miscarriage was compared . The results showed that compared with patients who received effective medication, the risk of miscarriage increased significantly in patients without intervention with a total total HR of 1.50 (95% CI 1.03–2.19, P = 0.04). However, the latest study needs to be interpreted with caution due to possible selection bias, different diagnostic criteria for SCH, and different definitions used for pregnancy outcome [19].

Taking into account the inconsistencies and limitations of available interventional studies, treatment with levothyroxine seems to be appropriate in women with a positive response to TPO when TSH levels exceed the reference range unrelated to pregnancy. However, there is insufficient data in the literature to initiate treatment with levothyroxine in women with a positive response to TPO with TSH levels from 2.5 to 4 Mme / l. In addition, based on a recent study on women with a negative reaction to TPO, treatment can only be recommended for TSH levels exceeding 4 Mme / l [18]. Current recommendations suggest treating SCH with levothyroxine during pregnancy in order to maintain TSH <2.5 Mme / l. On the other hand, studies show that an increase in TSH in pregnant women should be the upper limit of the reference pregnancy interval, rather than 2.5 Mme / l, and this can also be applied during pregnancy obtained after ART [18].

Currently, the benefit of levothyroxine treatment for pregnancy outcomes in women with euthyroid disease TAI both during spontaneous pregnancy and after ART is questionable.

In the case of ART, treatment with levothyroxine does not appear to be beneficial for TAI-positive euthyroid women. In specialized studies, there are no improvements in TAI-positive women who have undergone IVF [19]. These results were confirmed by RCTS in China, where treatment with levothyroxine compared to treatment with no levothyroxine did not reduce the frequency of miscarriages and did not increase the number of live births among women with normal thyroid function who tested positive for thyroid autoantibodies undergoing in vitro fertilization and embryo transfer [16].

The results of the TABLET study were also examined as part of the study. This multicenter, double-blind, randomized controlled trial examined the effects of levothyroxine at a dose of 50 mcg per day in women who tested positive for TPO-abs before conception. Treatment with levothyroxine did not lead to a higher rate of live births or pregnancy compared to placebo, which confirms the findings of previous RCTS [21].

Despite the low level of evidence, it is recommended to start treatment with any increase in TSH> 2.5 Mme / l before ART, given its potential advantages over minimal risk [17]. However, some potential dangers have recently been noted, indicating that excessive treatment of the thyroid gland in the mother in early pregnancy is associated with harmful effects on IQ and brain morphology in children in childhood [17]. Recently, there have been additional concerns that levothyroxine treatment may increase the risk of preterm birth, gestational diabetes, and preeclampsia [14].

Most authors agree that all patients seeking medical advice about infertility should be screened for the presence of an underlying thyroid disease, taking into account the potential harmful effect of thyroid dysfunction on the outcome of fertility. A thorough medical history and medical examination should be the first step before starting treatment. In addition to more obvious symptoms such as weight changes, fatigue, irritability, and heart palpitations, one should also pay attention to symptoms such as menstrual irregularities that may indicate thyroid dysfunction. The laboratory assessment should include at least TSH and TPO-abs.

In case of obvious thyroid dysfunction, appropriate therapy should be started immediately. SCH is best treated when TSH values exceed the normal upper value determined by population non-pregnant values, or in the absence of these control ranges with a fixed threshold of 4 Mme / l.

Taking into account the uncertainty in the literature regarding the harm-benefit ratio in patients with TSH cut-off levels of 2.5 to 4.0 Mme /, intervention in these cases should be limited and discussed with patients regarding the best available data. Currently, there is not enough time to start treatment with levothyroxine at pre-conception TSH levels of 2.5 to 4.0 Mme / l, especially in the case of ART.

Conclusion

The interaction between thyroid disease and fertility is complex. Open thyroid dysfunction often leads to menstrual disorders, fertility problems, and pregnancy complications, and therefore should be treated accordingly. There is currently little evidence to recommend treatment with levothyroxine with TSH levels between 2.5 and 4.0 Mme / l, given the possible side effects of overtreatment, especially in patients with mild thyroid dysfunction. We offer thorough longitudinal monitoring, especially in the presence of anti-thyroid antibodies among women undergoing ART. The 4 Mme / l limit for TSH appears as an intervention level for SCH treatment among women with and without TAI in ART.

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